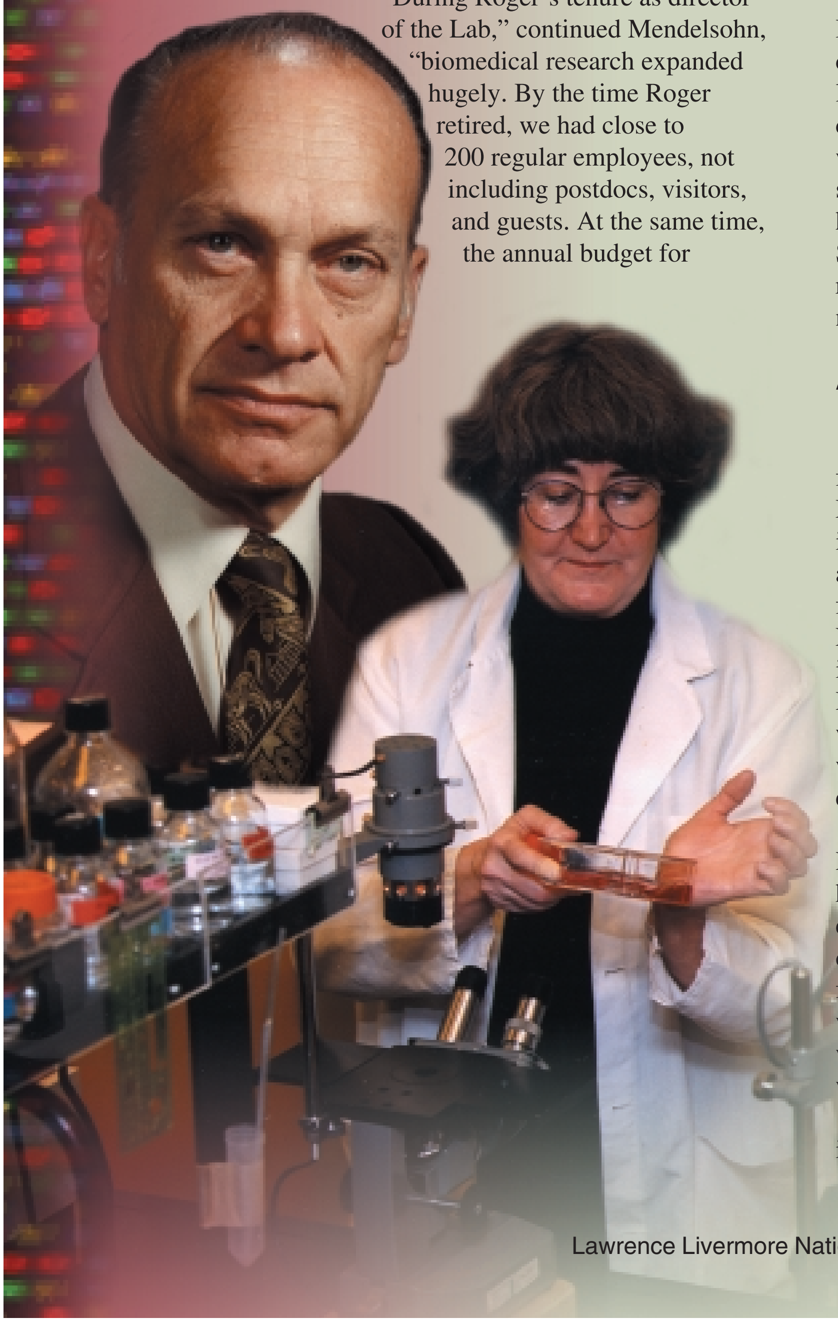
From Dosimetry to Genomics

ROGER BATZEL was the strong, silent type, just what the doctor ordered back in the early 1970s when Livermore's biomedical research program began to grow substantially. According to Mort Mendelsohn, associate director for Biomedical and Environmental Research from 1972 to 1992, "Roger was always there with whatever resources I needed to advance the program. He didn't talk a lot, but he was supportive in every way possible. And that's what mattered.

"During Roger's tenure as director of the Lab," continued Mendelsohn, "biomedical research expanded hugely. By the time Roger retired, we had close to 200 regular employees, not including postdocs, visitors, and guests. At the same time, the annual budget for biomedical and environmental research increased from $3.2 million to almost $30 million. The range of our research broadened and diversified just as much while he was in charge."



Roger Batzel brought Mort Mendelsohn to Livermore from the University of Pennsylvania. Mendelsohn had visited Livermore around 1970 as part of a site visit team. He met Batzel at that time as well as John Gofman, who had founded the biomedical and environmental programs at Livermore in 1963. Both Gofman and Mendelsohn were M.D.–Ph.D.s doing research on carcinogenesis and on radiation and its effects on chromosomes. In 1971, even before Batzel became director of the Laboratory, Gofman decided to leave Livermore. He recommended Mendelsohn to Batzel as his replacement.

Mendelsohn chuckles remembering his early meetings with Batzel. "Roger was a weaponeer, a Westerner, always wearing cowboy boots. I was very much the Eastern academic with long hair and a strong antiwar position. But Roger was very convincing when he talked about what a great place Livermore was to work and what opportunities were available. He was a super-salesman, which might sound negative. But everything he said was absolutely true. I started at Livermore in September 1972. Here I am, almost 30 years later, semi-retired, with almost no hair left, but still at Livermore. I've never regretted a moment of it."

An Emphasis on Biodosimetry

Biological research at the national laboratories began in 1954 with studies to determine the biological consequences of fallout radiation from the Bravo test at Bikini Atoll, in which Marshall Islanders and Japanese fishermen were seriously irradiated. As the need grew for a bioenvironmental presence at the Nevada and Pacific test sites and in Project Plowshare for peaceful applications of nuclear weapons, the Atomic Energy Commission mounted a small program at Livermore in 1963. John Gofman, a professor of medical physics at the Donner Laboratory of the University of California at Berkeley, was recruited to set up the new program. His initial charge was to study the dose to humans of radioisotopes in the environment.

Not long after Mendelsohn took over the program, Project Plowshare was discontinued, in part because of the potential health concerns associated with peaceful use of nuclear explosives. Researchers at Livermore continued to study the dose to humans. But the program became oriented toward finding biological measurements that indicated the dose to which subjects had been exposed. Prominent in this effort was developing a set of biological dosimeters for humans and, with it, the study of human radiation biology and toxicology.

With Batzel's encouragement, Mendelsohn became involved in the Radiation Effects Research Foundation

(RERF) in Hiroshima and Nagasaki, Japan, the primary organization that keeps tabs on the health of A-bomb survivors. Livermore invented the glycophorin-A assay and transferred it to RERF. The assay detects residual mutations in human red blood cells from exposure to radiation from nuclear bomb explosions decades earlier. No other mutation assay, before or since, has been able to reach back so far in time. Livermore and RERF researchers found that, on average, the mutant cells increase linearly with radiation dose.

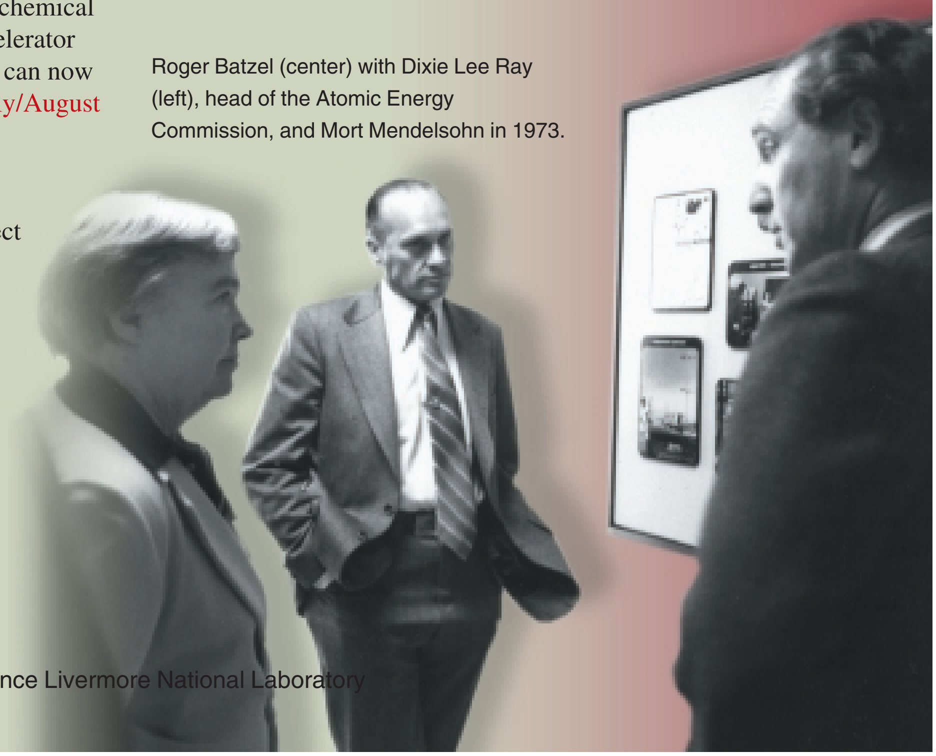
A second Livermore discovery in the mid-1980s greatly reinforced the use of chromosome aberrations as a dosimeter. It grew out of the human chromosome library project that Livermore and Los Alamos worked on jointly. With gene libraries for each human chromosome, researchers could paint chromosomes specifically. An otherwise obscure translocation (sharing of parts) between a painted and unpainted chromosome (or two chromosomes painted different colors) shows up as a two-color chromosome and can be viewed easily. Translocations could be identified 10 to 100 times faster than before, with greatly increased reliability. These chromosome aberrations also respond to radiation exposure and persist long enough to provide good dosimetry on A-bomb survivors.

And what of people who may be subjected to extremely small doses of radiation and have habits or participate in a lifestyle that may affect DNA? For example, nurses and x-ray technicians in hospitals or workers at nuclear reactors may receive regular miniscule doses. These people may also smoke or eat large quantities of red meat, both of which may affect DNA. In a 1992 interview, Mendelsohn expressed concern about whether biodosimetry methods would be able to sort out the results of such mixed exposures. This difficulty remains a problem. However, methods to attribute effects from chemical exposures are rapidly improving. With the use of accelerator mass spectrometry for biomedical research, scientists can now detect minute changes in human DNA (see *S&TR*, July/August 2000, pp. 12–19).

Beginnings of Biotechnology

The first successful molecular biotechnology project at Livermore took place in the late 1970s with the production of made-to-order monoclonal antibodies. (Antibodies are nature's defender molecules, and monoclonal means that they are produced by a single clone.) A scientist can select for and form single clones or copies of immunologically active cells. Such cells make only one antibody, and when isolated, they can be produced infinitely with complete purity and remarkable specificity. Two of Livermore's products are the monoclonal antibodies that recognize the subtle distinction

The foresight of Laboratory management in the 1970s and 1980s led to Livermore's major contributions to the Human Genome Project. Shown here is a scientist completing an early step in the gene sequencing process at the Joint Genome Institute in Walnut Creek, California, a collaboration of Livermore, Berkeley, and Los Alamos national laboratories.



Roger Batzel (center) with Dixie Lee Ray (left), head of the Atomic Energy Commission, and Mort Mendelsohn in 1973.

between normal and mutant red blood cells in the glycophorin-A assay. Other Livermore monoclonal antibodies can indicate whether a blood stain is human or whether a child has sickle cell anemia. Still others are useful for making the individual proteins involved in the complex process of repairing DNA.

Perhaps the most important antibodies to come out of this work were those to bromodeoxyuridine in DNA, a substance that can substitute for a normal building block of DNA. A small amount injected into a subject or in a culture will be synthesized into the DNA of any cells that are dividing. When this monoclonal antibody is coupled to a fluorescent marker, all the cells in division become fluorescent and can be seen under a microscope or detected and measured in a flow cytometer. A Livermore team used this technique and Livermore’s work in cell kinetics to develop methods that revolutionized the study of cell growth and that today are standard procedure worldwide. Cancer patients are routinely evaluated by these methods to see how fast their cancer cells are dividing.

Birth of the Human Genome Project

Says Mendelsohn, “My arrival at Livermore with new people, new equipment, and a new orientation coincided with a Laboratory-wide cutback. That was a difficult time at Livermore. But Roger was committed to the whole process and made my transition happen as smoothly as possible.”

One of the new people was Marv Van Dilla, a leading expert in flow cytometry, a technique for measuring and separating cells. From that beginning grew Livermore’s expertise in flow cytometry, which exploited the Laboratory’s knowledge of lasers and engineering as well as the biological sciences. Two years later, in 1974, Livermore scientists for the first time performed an experiment that successfully measured and sorted Chinese hamster chromosomes using flow cytometry. Not until 1979 did scientists learn how to do the same with human chromosomes, which are much smaller and more varied. By 1984, says Mendelsohn, “We had increased our proficiency and confidence in the method such that we could separately identify and study each of the human chromosomes. This ability, combined with worldwide developments in recombinant DNA technology, led to the Livermore–Los Alamos project to build human chromosome-specific DNA libraries.”

At about the same time, in 1984, Mendelsohn organized a meeting of molecular geneticists from around the world to brainstorm the potential for DNA-oriented methods to detect human heritable mutation in A-bomb survivors. It became clear to those at the meeting that despite the enormous scale of this effort, analysis of the entire human genome was feasible. In 1986, the Department of Energy was the first federal agency to launch a major initiative to completely decipher the human genetic code. A year later, Livermore researchers began to study all of chromosome 19, which they had earlier learned was the home of several genes important for DNA repair. In 1990, two years after Batzel retired, the Department of Energy joined forces with the National Institutes of Health

Early ground-breaking Livermore work in flow cytometry, a technique for separating specific cells from other cells that has come to have numerous medical research applications. Some biosensors to detect the specific agents used in biological weapons are based on flow cytometry.

to kick off the Human Genome Project, the largest biological research project ever.

Free Rein for Creativity

It is easy to wonder where Livermore's biomedical research program would be today if Roger Batzel had not been director during those formative years. Mendelsohn says, "When Roger chose people, he then gave them their own reins. Roger was a textbook example of a primary principle of Tom Peters: to never let management interfere with creativity."

—Katie Walter

Key Words: biotechnology, chromosome libraries, chromosome painting, dosimetry, flow cytometry, Human Genome Project, Roger Batzel.

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Livermore developed a way to "paint" specific chromosomes. With this technique, scientists can quickly identify chromosome aberrations. This photo is of one-day-old mouse embryos. The bright green chromosomes are chromosomes 1, 2, 3, and X. The orange one is chromosome Y.